STIC-ILL

Vol No

From: Yaen, Christopher
Sent: Tuesday, September 03, 2002 2:45 PM
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Dev Biol Stand 1992;74:323-39; discussion 340

Thromb Haemost 1995 Dec;74(6):1468-73

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1: Dev Biol Stand 1992;74:323-39; discussion 340

The effects of formulation and moisture on the stability of a freeze-dried monoclonal antibody-vinca conjugate: a test of the WLF glass transition theory.

Roy ML, Pikal MJ, Rickard EC, Maloney AM.

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285.

Deacetylvinblastine (DAVLB) hydrazide, a cytotoxic vinca alkaloid, has been linked to the monoclonal antibody, KS1/4, via aldehyde residues of the oxidized carbohydrate groups on the antibody. The resulting KS1/4-DAVLB DAVLB hydrazide conjugate is unstable in solution with both the acyl hydrazone linkage and the vinca moiety being subject to significant degradation, even at 5 degrees C. This necessitated the development of a freeze-dried formulation of the antibody-drug conjugate. Formulation factors considered were pH, ionic strength, buffer, excipient types, and excipient ratios. A formulation with equal weight ratios of mannitol, glycine, and conjugate in a low ionic strength phosphate buffer at near neutral pH was selected. Stability was studied at various moisture levels (1.4%, 3.0%, and 4.7%) and temperatures (5 degrees C, 25 degrees C, and 40 degrees C). Degradation was measured by size exclusion HPLC (aggregate formation) and by reverse phase HPLC (hydrolysis of hydrazone linkage and vinca decomposition). Differential scanning calorimetry (DSC) indicated that all samples were above their glass transition temperatures, Tg, when stored at 40 degrees C. When stored at 25 degrees C, only the highest moisture sample was initially above its Tg. However, due to crystallization of the excipients during storage and the resulting decrease in Tg, samples stored at 25 degrees C were also above their Tg during much of the storage period. The degradation rate, R, increased sharply with increasing temperature and with increasing moisture level. Degradation kinetics obeyed the Williams-Landel-Ferry relationship, $R/Rg = \exp[k(T-Tg)]$, where Rg is the degradation rate at Tg. For all three moisture levels and all three degradation pathways, $k = 0.143$.

PMID: 1592182 [PubMed - indexed for MEDLINE]

Pharmacokinetics and tolerance of the natural pentasaccharide (SR90107/Org31540) with high affinity to antithrombin III in man.

Boneu B, Necciari J, Cariou R, Sie P, Gabaig AM, Kieffer G, Dickinson J, Lamond G, Moelker H, Mant T, et al.

Laboratoire de Recherche sur l'Hemostase et la Thrombose, Toulouse, France.

This paper reports the results of the first administration of the synthetic natural pentasaccharide with high affinity to antithrombin III (NP) in man. This study was mainly focused upon the pharmacokinetic properties and general tolerance of the compound. Subcutaneous injections of doses < 1.43 mg (1000 anti Xa IU) did not generate measurable anti-Xa activities. After subcutaneous injection of increasing doses from 1.43 to 22.9 mg (1000 to 16,000 anti-Xa IU) to young healthy volunteers, it was found that the maximal concentration (Cmax) and the area under curve (AUC) were linearly correlated to the dose, that the total plasma clearances (CI) were constant and almost 3 times lower than those of the current low molecular weight heparins. Cmax were reached between 1 h and 3 h after the injection and the half-lives (t 1/2) were remarkably constant (13.1 h to 13.9 h). During the first 24 h following the injection, around 50% of the total administered dose was recovered in the urine in an active form, indicating that kidney plays a major roles in the elimination of NP. Consistent with these results, when NP was administered to healthy elderly volunteers having a lower creatinine clearance, the half-life of the compound was longer and the clearance lower. At doses exceeding 22.9, Cmax, and AUC were slightly lower than expected, the percentage of the dose recovered in the urine and the total apparent plasma clearance increased, suggesting that the excess of NP unbound to antithrombin III was excreted faster. NP was also administered at various dosages once or twice a day for 7 days to 20 elderly volunteers. Due to the long half-life of the compound the "steady state" was obtained 2 to 3 days after the first injection at which the mean Cmax was increased 1.5 to 2 times. The general tolerance of the compound was excellent. No relevant prolongations of the prothrombin time, of the activated partial thromboplastin time or of the bleeding time were observed.

A re-bleeding phenomenon of the bleeding time incision, probably related to friability of the haemostatic plug, occurred in 3 subjects treated with the highest dose regimens: single injection of 26.6 mg (20,000 anti-Xa IU) (young volunteers) and repeated injections of 11.4 mg (8,000 anti-Xa IU) once a day for 7 days (elderly volunteers). At these times, plasma NP concentrations were between 2.9 and 3.6 micrograms.ml-1 (2 and 2.5 anti-Xa IU.ml-1).

Publication Types:

- Clinical Trial
- Clinical Trial, Phase I
- Randomized Controlled Trial

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